fractions against 69.1 Gy/32 fractions in the IMRT group. Endpoints were local control, acute and late toxicity.
Results A. Interim analysis (n = 150) showed low rates of moist desquamation, mostly located in the infra-mammary fold (5/75 WBI-SeqB vs 3/75 WBI-TDP-SIB, p =0.5). Trends in favor of WBI-TDP-SIB were observed for breast edema (p=0.08) and pruritus (p = 0.1). B. The volume of normal tissue receiving 4 Gy, 6 Gy and 8 Gy was at least 3, 6 and 13 times smaller in the DP-8Gy arm compared to Conv-8Gy and DP-16Gy (p<0.05). DP-8Gy resulted in a pain response of 80% compared to 53% and 60% for Conv-8Gy and DP-16Gy. Quality of life analysis suggests better outcome for patients treated in the DP-8Gy arm with the scores 'painful characteristic', 'insomnia' and 'appetite loss' reaching significance (p<0.05). C. Local control at 5 y was 83.4% and 75.2% in the DP- and IMRT-treated patients, respectively (p=0.28). Grades of acute dysphagia and mucositis were higher for the DP- than for the IMRT-treated group (p=0.03 and p=0.08, respectively) but differed according to DP-technique and –prescription. Poorly healing mucosal ulcers at the locations of the highest doses were observed in 9 DP- and 3 IMRT-treated patients (p=0.07) and reflect dose-limiting toxicity (DLT). Analysis of all DP-treated patients showed that DP-planning using a linear relation between 18F-FDG voxel-intensity and dose was associated with high risk of DLT if peak-doses were >84 Gy or the volume receiving >80 Gy was >1.75 cc in 30-fraction schedules (OTT = 6 weeks). Discussion and conclusions
The term DP covers a variety of techniques that open a vast spectrum of applications.The use of TDP after breast-conserving surgery allows to integrate boost treatment in WBI without increasing toxicity. In bone metastasis, DP-8Gy was selected as a candidate experimental arm to test the hypothesis of improved palliation by reducing the irradiated volume. A confirmatory phase III trial is underway. In loco-regionally advanced head&neck cancer, DP may open a window for improving local control. However, the safety margin for dose-escalation is narrow. Poorly healing mucosal ulcers at the peak-dose regions are DLT of DP. The dose/volume/DLT relationship casts doubt on the safety of linear 18F-FDG voxel-intensity based DP. A phase III trial using non-linear DP is underway. Tumor heterogeneity – known for decades- supports DP and refutes the use of homogeneous dose distributions. Dose escalation to radioresistant regions in the tumor or decreasing the irradiated volume may be a conceptually naive way to use DP. The insight that ionizing radiation can enhance vascular and immunogenic mechanisms of cell death opens a new field for DP characterized by large fraction doses to small sub-volumes of tumor. In these applications, direct cancer cell kill might be subordinate to other goals of DP including amplifying bystander and abscopal effects or breaking immune tolerance. Combination of DP with immunomodulating drugs or drugs that target vasculature or immune checkpoints are investigated to validate these concepts.

SP-0521
The biological rationale of dose painting: is it realistic?
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Any additional dose that can be applied without harm will lift tumour control in a patient population. Dose painting (DP) claims to make better use of dose than an indiscriminate or random escalation: by virtue of functional imaging, it should be more effective, more selective and more patient-specific. Still, on a pragmatic level, DP can often be summarized by "we boost because we can". What does it take to go more biological?
Obstacles lie in quantitative functional image acquisition, image interpretation, dose prescription and collection of evidence. Unfortunately, quantitative functional imaging is notoriously capricious. The problems tend to grow the more specific in terms of tumour biology an imaging modality is - which is one of the reasons for the popularity of FDG-PET, being arguably one of the least specific modalities. A specific modality may be more intriguing scientifically, but obviously shows only a narrow aspect of tumour biology, which may create a need for a combination of multiple modalities. Imaging modalities usually operate at length scales far greater than the phenomena to which they are sensitive. This can make the interpretation of images challenging, especially when tracer kinetics need to be considered. Imaging sophistication alone reveals little of the import of some physiological or biological trait for treatment outcome. Only clinical data can fill this gap in biological understanding with some confidence. Further, a single image is just a snapshot of a dynamically evolving tumour, and if taken pre-treatment, says little about the tumour´s response to therapy. Therefore, without any highly suggestive clinical evidence, the prospects for naive (i.e. model-based) DP are bleak.
Accordingly, the majority of DP trials to date are pragmatic in their choice of imaging modality and –protocol, and dose prescription. In addition to being practical, especially in a multi-centric setting, this also ensures that a proof of benefit (of both boosting and imaging) can eventually be made. The essential advantage of "we boost because we can" over sophisticated "dose painting by numbers" is, that it generates the data needed to reach said sophistication.
From this pragmatic standpoint, neither today´s imaging capabilities nor the understanding of their relevance to tumour treatment response are sufficient to speak of an established biological rationale for DP. Some clinical evidence exists in few instances that links certain functional imaging to lack of tumour control or even location of recurrence. Given this, workable DP concepts today are rather shaped by considerations about image sensitivity and specificity and organ mobility, than biology.

SP-0522
Dose prescription and treatment delivery at the voxel scale: a fantasy?
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Purpose/Objectives: This work aims at formally identifying the methodological issues that hinder the implementation and adoption of dose painting (DP) in radiotherapy. DP entails the use of functional imaging to set up a non-uniform dose escalation, either with sub-contours or voxel-to-voxel variations. Although theoretically appealing, DP has not succeeded yet in passing from research to clinical use. This work reviews the physical, mathematical, and statistical causes of this delay, in the specific case of DP guided by PET.

Method: The following steps occur in PET-based DP: acquisition of PET images (before and/or during treatment, with one or several tracers), conversion of the uptake(s) into a dose increment, treatment plan optimization, fractionated treatment delivery, accumulation and assessment of the delivered dose, and optional treatment adaptation. Every step or piece of data in this path can be modeled to investigate its shortcomings. All PET tracers are characterized with their specificity and sensitivity as a surrogate of some biological variable of interest in given conditions (e.g., before or during radiotherapy). PET images are described by their resolution and signal-to-noise ratio. Treatment plan quality is assessed by a quality-volume histogram (QVH), namely, a DP-specific dose-volume histogram that considers the ratio planned dose over prescribed dose. Random and systematic patient setup errors are quantified with their respective standard deviation. Non-rigid registration of pre- and per-treatment images is used to approximate the cumulated dose, taking into account patient evolution (tumor regression, possible weight loss).

Results: Our main result is the formal proof that PET-based DP cannot lead to a delivered dose that is strongly correlated with the tracer uptake at the microscopic level. This weak correlation is caused by: i) The limited information conveyed by heterogeneities observed in PET images. Current PET systems have a low resolution and a low signal-to-noise ratio,